REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Upon entry of the amendments, claims 26-28, 31-36 and 38 will be pending in the application. Claims 1-25, 29 and 37 are being canceled without prejudice or disclaimer, and no new claims are being added at this time. Claims 26-28 and 31 presently are being amended. The amendments to those claims do not introduce new matter into the application. In particular, exemplary support for the amendment to claim 26 exists in original claim 30 and in paragraph 0040 of the specification. Exemplary support for the amendment to claim 31 exists in paragraph 0039 of the specification.

II. Election of Invention

The examiner restricted the invention into two groups: Group I includes claims 1-25, drawn to a method of treating or preventing breast cancer, and Group II includes claims 26-38, drawn to a pharmaceutical composition for percutaneous administration. In response, Applicants made an oral election on April 20, 2006 to prosecute Group II.

Applicants now affirm their election of Group II for prosecution.

III. Oath/Declaration

The Office Action stated that a "statement over each applicant's signature providing a complete post office address of each applicant is required." Applicants submit that that they already have submitted such a statement.

The Declaration and Power of Attorney filed on October 19, 2004 contains the signatures and addresses of all three inventors.

IV. Claim Objection – Claim 31

The Office Action objected to claim 31 because the word "vehicle" was misspelled. Applicants have corrected the misspelling, and therefore request withdrawal of the objection.

V. Claims 26-27 Are Patentable Over U.S. Patent No. 5,904,930

Claims 26-27 were rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by U.S. patent No. 5,904,930 ("Fischer"). Applicants traverse the rejection.

Fischer does not teach or suggest a composition containing a fatty acid ester penetration enhancer, as recited by claim 26. Accordingly, the anticipation rejection should be withdrawn.

VI. Claims 26-27 Are Patentable Over Suavez et al., Carcinogenesis 1999

Claims 26-27 were rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Suavez et al., Carcinogenesis, 20(5); 843-850 (1999) ("Suavez"). Applicants traverse the rejection.

Suavez does not teach or suggest a composition containing a fatty acid ester penetration enhancer, as recited by claim 26. Accordingly, the anticipation rejection should be withdrawn.

VII. Claims 26-27 Are Patentable Over U.S. Patent No. 4,919,937

Claims 26-29 were rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by U.S. patent No. 4,919,937 ("Mauvais-Jarvis"). Applicants traverse the rejection.

Mauvais-Jarvis does not teach or suggest a composition containing a fatty acid ester penetration enhancer, as recited by claim 26. Accordingly, the anticipation rejection should be withdrawn.

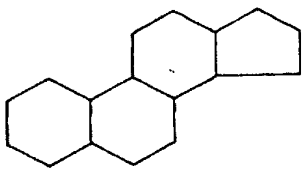
VIII. Claims 30-34 and 36 Are Patentable Over Mauvais-Jarvis and German Patent Application No. DE 3836862

Claims 30-34 and 36 were rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Mauvais-Jarvis in view of DE 3836862 ("Gunther"). According to the rejection, Mauvais-Jarvis describes hydroalcoholic gels for percutaneous administration of 4-hydroxy tamoxifen, but does not teach using a fatty acid ester penetration enhancer in such gels. Gunther allegedly "teaches that fatty acid esters ensure adequate penetration of [steroids] through the skin for therapy, and that a preferred fatty acid ester is isopropyl myristate." The rejection asserts that it was obvious to use the isopropyl myristate of Gunther in the 4-hydroxy tamoxifen gel of Mauvais-Jarvis. Applicants traverse the rejection.

The rejection relies on an overly simplistic view that penetration enhancers work interchangeably with different active agents and in different formulations. In fact, the selection of a penetration enhancer is not so simple. To this day, skilled artisans cannot predict whether a particular penetration enhancer will work for a particular active agent in a particular formulation.

A 2004 article that appeared in Nature Biotechnology[1] (copy attached) reviewed this issue and noted that investigations of hundreds of potential chemical penetration enhancers over the past 40 years have generated much fanfare, yet yielded little useful knowledge for predicting a penetration enhancer's performance. As described in the article, the problem arises from a complex diversity of ways that penetration enhancers may modify the stratum corneum. For instance, enhancers can alter the intercellular domain by fluidization, polarity alteration, phase separation or lipid extraction. Additionally, enhancers may act on protein structures to split the stratum corneum, denature keratin or form vacuoles within corneocytes. The complexity of such interactions makes it such that "we still cannot predict *a priori* those safe enhancers that will work for named drugs under clinical conditions."[2] Accordingly, the selection of penetration enhancers for transdermal formulations requires time-consuming experimentation.

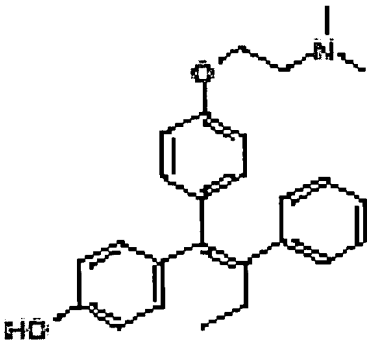
Given the state of the art, Gunther's report that isopropyl myristate facilitates transdermal administration of steroids (specifically, gestodene and estradiol) would not have suggested to skilled artisans that isopropyl myristate facilitates transdermal administration of 4-hydroxy tamoxifen. 4-Hydroxy tamoxifen is not a steroid. Steroids and 4-hydroxy tamoxifen differ significantly in nature and composition. Steroids are chemically based on a fundamental saturated tetracyclic hydrocarbon known as a sterane. Sterane, however, does not exist in the chemical structure of 4-hydroxy tamoxifen. In fact, 4-hydroxy tamoxifen lacks any structure even akin to that of sterane. This is apparent from the chemical structures of sterane and 4-hydroxy tamoxifen shown below.



Sterane

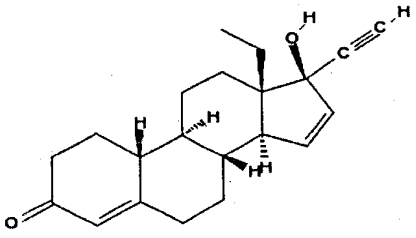
[1] Barry, Breaching the skin's barrier to drugs, Nature Biotechnology, 22(2): 165-167 (2004).

[2] Id. at 166.

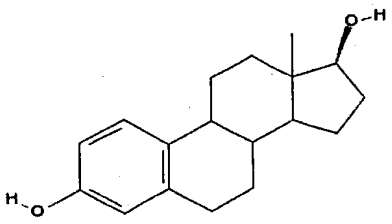


4-Hydroxy Tamoxifen

By contrast, the tetracyclic structure of steroids is apparent in the gestodene and estradiol compounds that Gunther described using, as shown below:



Gestodene



Estradiol

Thus, it is clear that Gunther used the word "steroid" conventionally, in reference to the class of compounds containing the sterane backbone. It is also clear that 4-hydroxy tamoxifen is not in that class.

Even if it were the case that Gunther's success with transdermal steroid delivery made it obvious to try isopropyl myristate as a penetration enhancer for 4-hydroxy tamoxifen, which it did

not, the fact would remain that "obvious to try" is not the proper standard for evaluating obviousness. *Hybritech, Inc. v. Monoclonal antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 107 s. Ct. 1606 (1987).

For at least the foregoing reasons, the obviousness rejection should be withdrawn.

IX. Claims 35 and 37 Are Patentable Over Mauvais-Jarvis, Gunther and U.S. Patent No. 5,720,963

Claims 35 and 37 were rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Mauvais-Jarvis in view of Gunther and further in view of U.S. patent No. 5,720,963 ("Smith"). The rejection applies Mauvais-Jarvis and Gunther as described in the previous section, but further alleges that Smith describes adjusting the pH of topical treatments as recited in claims 35 and 37. Applicants traverse the rejection.

Smith does not cure the deficiencies of Mauvais-Jarvis and Gunther described above. Accordingly, the obviousness rejection should be withdrawn.

X. Claim 38 Is Patentable Over Mauvais-Jarvis, Gunther and U.S. Patent No. 6,013,270

Claim 38 was rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Mauvais-Jarvis in view of DE 3836862 ("Gunther") and further in view of U.S. patent No. 6,013,270 ("Hargraves"). The rejection applies Mauvais-Jarvis and Gunther as described above, but further alleges that Hargraves describes a dispenser for a skin care composition as recited in claim 38. Applicants traverse the rejection.

Hargraves does not cure the deficiencies of Mauvais-Jarvis and Gunther described above. Accordingly, the obviousness rejection should be withdrawn.

X. Concluding Remarks

This application is in allowable condition, and Applicants respectfully request an early indication to this effect. If the Examiner believes that any issue requires further consideration, she is invited to contact the undersigned directly.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or

even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 8/7/06

By Todd Spalding for 55,638

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Breaching the skin's barrier to drugs

Brian W Barry

A novel approach for identifying synergistic mixtures of skin penetration enhancers promises to transform development of transdermal products, including patches.

The skin has evolved to minimize entrance of noxious chemicals and UV radiation into the body. But from a pharmacological perspective, delivering drugs across the skin is an important goal. Transdermal delivery would avoid numerous problems with the oral route, including drastic pH changes, the deleterious presence of food and enzymes, variable transit times, pulse entry (rapidly fluctuating drug plasma concentrations), side effects and inadequate patient compliance, while also eschewing needle delivery and its associated inconvenience and even patient phobia. In this issue, Karande *et al.*[1] describe the identification of mixtures of nonirritant enhancers that essentially remove the skin's barrier to 10 kDa macromolecules—a major breakthrough in transdermal drug delivery.

Recently, the transdermal route has competed with oral therapy for the accolade of the most innovative research area for drug delivery. Yet the market for transdermal patches, for example, comprises only a few traditional low molecular weight drugs controlling motion sickness, cardiovascular conditions, sex hormone depletion, contraception, smoking or pain. The paucity of candidates for such delivery arises because few molecules yield skin permeability coefficients sufficiently high to develop clinically active plasma levels. Additionally, as Karande *et al.* point out, simple, unassisted transdermal drug delivery is even less applicable for large hydrophilic molecules because of their very low skin permeation rates. The question arises: how can we change the drug formulation, or the skin barrier, to achieve satisfactory plasma levels without damaging the skin—an organ particularly susceptible to irritant, allergic and sensitization reactions?

Molecules have three potential pathways from the skin surface to viable tissues: through sweat ducts, via hair follicles or across the intact stratum corneum enclosing them. Because of its fractional area (99.9%), the continuous stratum corneum provides the major barricade and is therefore the usual target for attempts to increase drug delivery. Its 'brick and mortar' structure comprises dead corneocytes of hydrated keratin embedded in multiple lipid bilayers of ceramides, fatty acids, cholesterol and cholesterol esters. Such bilayers construct a complex mixture of crystalline, semi-crystalline, gel and liquid crystal interconnecting domains (Figure 1 shows a simple structural representation). As most molecules penetrate the skin using this intercellular microroute, many techniques aimed at enhancing drug delivery bypass or temporarily disrupt its elegant molecular structure[2].

Simple formulation approaches that concentrate on the interaction of medicament and vehicle (without modifying significantly the intercellular matrix) start with selecting the correct drug or prodrug from a pharmacological class or congeneric series. Essentially, the molecule should display suitable physicochemical properties for it to translocate quickly across the horny layer. Ideally, it should have a low molar mass (preferably <0.6 kDa), adequate solubility in oil and water (correlating with a low melting point) and a high, optimal partition coefficient. Prodrugs additionally require suitable enzymes in the viable tissues to generate active species. The chemical potential should be maximal (a saturated solution or suspension is used); supersaturated systems further increase permeation. Ion pairs, complex coacervates and eutectic systems have limited potential.

However, for troublesome permeants, such as those considered by Karande *et al.*, formulators move to more advanced approaches. They entrap the drug within vesicles or particles and target skin layers or the circulation. Liposomes have been much investigated for cutaneous delivery as for other routes. A controversial approach deploys 'transfersomes'—vesicles that incorporate molecular 'edge activators.' Their inventors claim that, being ultradeformable (up to 10^5-fold more deformable than a normal vesicle), they squeeze through micropores in the stratum corneum[3]. Competitive formulations include 'ethosomes' and 'niosomes.' The former are liposomes high in ethanol content; niosomes use nonionic surfactants to construct vesicles. The PowderJect system—PowderJect (Oxford, UK) is now a subsidiary of Chiron (Emeryville, CA, USA)—fires solid microparticles through the corneum impelled by a supersonic shock wave of helium (although work on systems other than vaccines is now in abeyance), whereas Weston Medical's (Cambridge, UK) Intraject device delivers liquids.

More recent tactics bypass or remove the horny layer. A device with 400 microneedles inserts drugs just below the barrier. Using chip fabrication technology, solid silicon needles (coated with drug) or hollow metal needles (filled with solution) increase fluxes by up to five orders of magnitude[4]; feedback control is a possibility. More drastically, the horny layer can be ablated using chemical peels, microdermabrasion with aluminum oxide crystals, dermabrasion with motor-driven cylinders, lasers, adhesive tape stripping or epidermatomes.

A fourth approach uses electrically assisted methods. Low-frequency ultrasound disturbs the lipid packing in the microroute as shock waves from collapsing vacuum bubbles increase the free volume space in bimolecular leaflets and thus enhance drug penetration by

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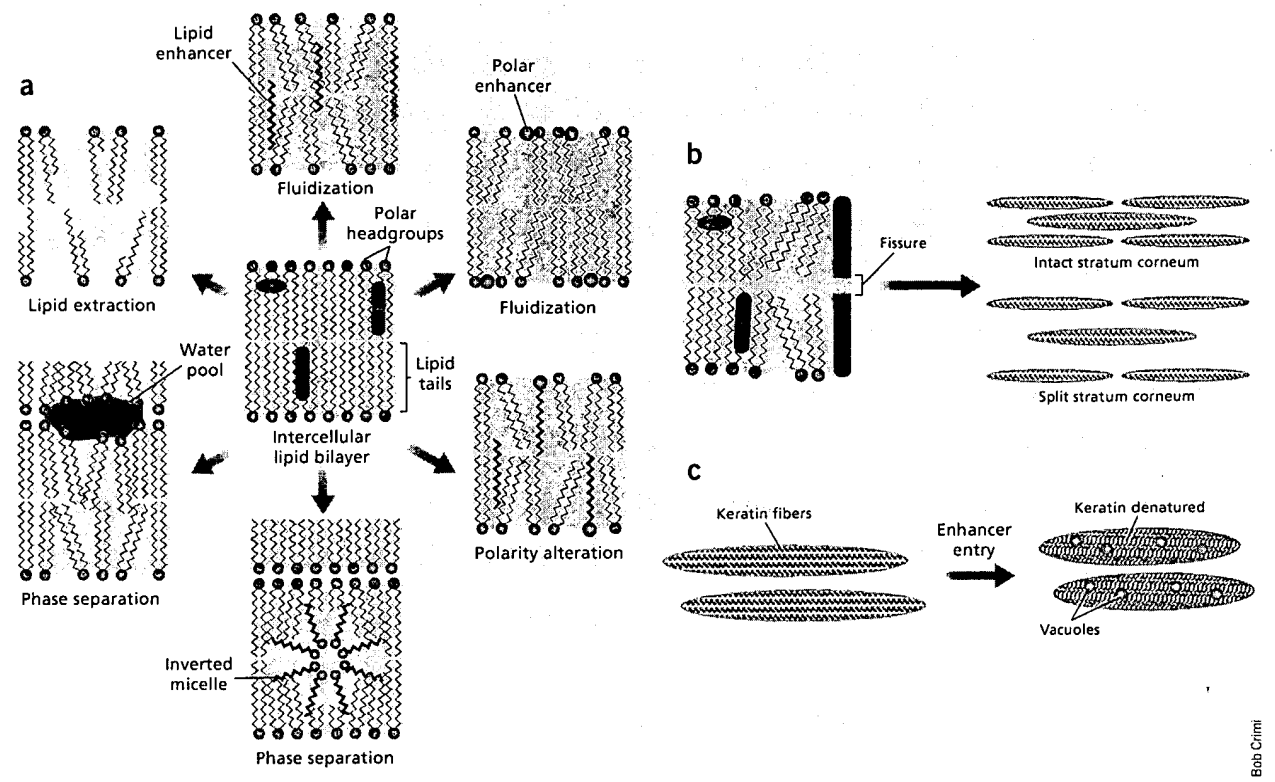

Figure 1 Getting under your skin. (**a**) Action at intercellular lipids. Some of the ways by which penetration enhancers attack and modify the well-organized intercellular lipid domain of the stratum corneum. (**b**) Action at desmosomes and protein structures. Such dramatic disruption by enhancers (particularly potent solvents) as they split the stratum corneum into additional squames and individual cells would be clinically unacceptable. (**c**) Action within corneocytes. Swelling, further keratin denaturation and vacuolation within individual horny layer cells would not be so drastic but would usually be cosmetically challenging. (See Menon *et al.*[10] for further details.)

up to 1,000-fold[5]. Iontophoresis (at about 0.5 mA/cm^2) boosts molecular transport mainly by electrorepulsion, or by electroosmosis or current-induced changes within the lipid structure[6]. Skin electroporation is more dramatic, creating transient aqueous pores using micro- to millisecond pulses of 100–1,000 V/cm. Fluxes increase by up to 10,000-fold for neutral and highly charged molecules of up to 40 kDa[7]. Limited work has tested the ability of magnetic fields to move diamagnetic materials through skin; Langer[8] considered using intelligent systems based on microchip technology to deliver drugs in controlled, pulsatile mode. Laser pulses supply photomechanical waves to stress the horny layer. The latest device generates radio frequency waves, forming microchannels through the stratum corneum beneath densely spaced microelectrode arrays.

All these methods require an electrical apparatus; they are not validated for effectiveness and patient safety and are unsuitable for routine home use. But one final technique remains—the oldest one of all.

Incorporation of chemical penetration enhancers into topical formulations has been applied in drug delivery since the sixties (such accelerants can also be combined with electrical methods[9]). Karande *et al.* propose a novel approach to this established technology. Ideally, enhancers exhibit the sole property of reversibly reducing the barrier of the stratum corneum without inducing clinical effects, including irritation. Hundreds of formulations have been investigated since the archetypical aprotic solvent DMSO was introduced forty years ago, to much dermatological excitement. Yet we still cannot predict *a priori* those safe enhancers that will work for named drugs under clinical conditions, although simple guidelines have been proposed[2].

The fundamental problem may be appreciated by considering just some of the complex ways in which different enhancers may modify the stratum corneum. Figure 1 illustrates how accelerants can alter the intercellular domain by fluidization, polarity alteration, phase separation or lipid extraction[10]. Potent enhancers may also act at desmosomes and other protein structures to split the stratum corneum, denature keratin or form vacuoles within the corneocytes. Many powerful enhancers combine several such processes. The complexity of such interactions in a biological tissue militates against *in silico* predictions; multiple skin experiments are necessary to develop formulations and satisfy drug regulatory bodies. Such a blunderbuss approach can be a time-consuming undertaking.

We do know, however, that enhancer mixtures are more efficient than single chemicals. The method of Karande *et al.* screens over 5,000 putative synergistic mixtures 100-fold more effectively than do current tools. The library of candidate enhancers was a third of a pool of about 100 chemicals—a reasonable, practical reduction. The authors discovered rare mixtures of enhancers that increase the skin permeability to macromolecules such as heparin, leutenizing hormone releasing hormone and an oligonucleotide by up to 100-fold, without inducing skin irritation.

Minor drawbacks to the work were that the authors used porcine and not human skin.

Species differences are particularly noteworthy when drugs permeate skin, although pigskin is more comparable to human skin than many other animal tissues. The method used an electrical measurement to quantify impairment of the lipid barrier. It assumed that skin impedance changes would correlate with alterations to drug permeation, independently of the medicament of interest, a reasonable but not perfect assumption.

In future work, it would be valuable to elucidate exactly why the areas of hot spots in potency were so restricted and the fundamental molecular mechanisms responsible for the enhancing action. Whatever the mechanism, the real challenge will be whether, within the next 10 years, topical drug preparations originating from this innovative approach can clear regulatory approval and make it to the clinic—a skin-tingling prospect indeed!

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2. Barry, B.W. *Eur. J. Pharm. Sci.* **14**, 101–114 (2001).
3. Cevc, G. Crit. Rev. Ther. Drug Carrier Syst. **13**, 257–388 (1996).
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Phage-inspired antibiotics?

Steven Projan

Rather than using bacteriophage themselves as treatments, a new approach recruits them in the search for antibiotics with new antibacterial mechanisms.

Since their discovery, bacteriophages have been viewed not only as important genetic but also as potential antibacterial therapeutics—a promise that has yet to be effectively realized[1]. In this issue, Liu *et al.* [2] scour the genomes of a host of bacteriophages from *Staphylococcus aureus* for gene products that inhibit the bacterium, and in so doing identify novel targets for antibacterial agents. The premise of the authors is that bacteriophages have evolved multiple strategies to interfere with bacterial growth and, rather than using bacteriophages themselves as antibacterial agents, the phage products could be used to validate targets, develop screens and even form the basis of novel small molecule therapeutics.

Altogether, Liu *et al.* have sequenced 26 *S. aureus* bacteriophage genomes, and in their paper they identify 31 proteins or polypeptides that inhibit the growth of the bacterium (Fig. 1). The examples provided by the authors show that many of these phage proteins target DNA replication and RNA transcription (already well-appreciated antibacterial targets). The most important aspect of this work, however, is that the authors were able to use the biochemical interaction between a phage-derived protein and its bacterial target to develop a novel high-throughput screen to identify small molecules that could inhibit bacterial growth via the same mechanism as the phage protein. The authors are still in the early stages of their work, but they are off to a promising start in their quest. Yet what of the original goal of using bacteriophage themselves as therapeutics? The authors themselves speak of a 'renaissance' of this approach.

Bacteriophage therapy for bacterial infections has almost a cult-like following. Proponents argue that such a strategy is more 'natural' than small molecule, 'magic bullet,' chemotherapy. The mantra goes: bacteriophages are easy to find, they can rapidly kill target bacteria with little emergence of resistance (which could be bypassed by using 'phage cocktails' anyway) and as bacteriophages are so easily propagated, this therapy should be quite inexpensive (certainly cheaper than small molecule chemotherapy). What's not to like? And why haven't we witnessed more progress toward the use of bacteriophages as therapeutic agents?

One of the most compelling aspects of antibacterial research is that we have at our disposal many animal models of infection that are quite predictive of human clinical outcomes. These range from straightforward (and fast) intraperitoneal challenge models with death as an endpoint to the 'gold standard' of infectious endocarditis models. It is typical to see publication of multiple *in vivo* studies evaluating the efficacy of a novel class of agents in such models early in the development process. The idea of phage therapy is now virtually a century old and what little animal efficacy data there is in the literature can charitably be described as meager. A single recent publication describes efficacy using a strain of *Enterococcus faecium* in an intraperitoneal challenge experiment[3]. This silence speaks volumes. Indeed the personal, anecdotal testimonials of former patients who 'benefited' from phage therapy is both amusing and sad—we do not hear from those patients whose infections were not cured, for obvious reasons.

One of the reasons that small molecules work is that those that we commonly use have been selected (with much effort) to have appropriate levels of distribution in human tissues, appropriate half-lives in those tissues and other key pharmacokinetic properties. Even proteins, which are on the order of 100-fold more complex than small molecules, must be held to the same type of pharmacokinetic rules. However, bacteriophage are at a level of complexity that dwarfs that of therapeutic proteins[4]. Their massive size (compared with small molecules) suggests poor tissue distribution and pharmacodynamic and immunogencity issues galore, the idea of a single dose of bacteriophage not withstanding.

As almost any biology student (and even a few venture capitalists) can tell you, the basis of the Luria-Delbruck fluctuation test (which showed that mutations are spontaneous, not induced) is that bacteria naturally and readily develop resistance toward bacteriophages. In round figures, this happens at about a frequency of 10^{-6}. Indeed, most strains of a given pathogenic bacterium are already naturally resistant to most bacteriophages that target that species. This basically puts bacteriophages on a par with the worst of small molecule bacterial therapeutics and would render them unusable for treating most systemic infections, which routinely involve a minimum of 10^9 organisms. This is why those who believe in phage therapy blithely tell us that all we need to do is use a 'cocktail' of bacteriophage in much the same way we use combinations of drugs for tuberculosis or HIV infection. It is agreed that a combination approach is a given if phage therapy is to work, but such a strategy also

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